Efficacy of single dose antihistamine vs. single dose valerian-hops in subjective sleep measures among war refugees: a comparison trial

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Abstract

Background: Many sedatives and anxiolytics are used in single dose or chronically to aid sleep. Clinically important sedatives include valerian-hops and antihistamines as they are used over the counter and are highly accessible and safe agents. **Objectives:** To evaluate and compare a single dose of chlorpheniramine versus valerian-hops combination in modulating subjective sleep measures in insomniac war refugees. **Methods:** Insomnia among refugees was screened using the Insomnia Severity Index (ISI). Insomniac subjects were randomized to received a single dose valerian-hops (320/80 mg) (n = 65), or chlorpheneramine (4 mg) (n = 50) or placebo (n = 76) two hours prior sleeping. Participants were instructed to complete Leeds Sleep Evaluation Questionnaire (LSEQ), visual analogue scales of anxiety and sedation. Also sleep latency, total hours slept and self-rated improvement were obtained. **Results:** Almost 75% of screened refugees had insomnia. Chlorpheneramine reduced sleep latency and anxiety significantly, however it resulted in poor sleep quality. Valerian-hops group showed marked anxiolysis one hour after dosing, a sleep quality similar to placebo and better than chlorpheneramine, and better alertness compared to placebo. Participants satisfaction was higher with chlorpheneramine and there was no difference in the total hours slept. **Discussion:** Valerian-hops combination may provide better sleep quality than antihistamines.

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Introduction

Insomnia is a primary sleep disorder whereby patients have difficulties falling asleep, with maintaining sleep during the night, or with early wakening[1].

It is estimated that more than 30% of the populations of industrialized countries report sleep disturbances[2,3]. Improper sleep has a negative impact on one's health-related quality of life and impairs patients' social, physical and cognitive functioning[4].

According to the 2012 report of the United Nations High Commissioner for Refugees (UNHCR), there were 15.4 million refugees worldwide[5].

Refugees are highly predisposed to developing neurological and psychological disorders such as anxiety, depression and post-traumatic stress disorder[6,7].

Surprisingly, insomnia prevalence and treatment is seldom studied in refugee populations. Two recent studies reported insomnia prevalence of 38% and 44% among displaced people[6,8].

Benzodiazepines and sedating antihistamines are among the most prescribed sedative hypnotics for both chronic use or when needed as a single dose[9].

Although these synthetic medications have proved their efficacy in sleep induction, they are associated with side effects such as dizziness, headache, dependence and tolerance[10,11]. Therefore, alternative therapeutic options such as valerian root have increased in popularity.

Valeriana officinalis is a hardy perennial flowering plant[12]. It is native to Europe and parts of Asia and has been naturalized in North America for commercial use. Valerian root is formulated as tablets or soft gelatin capsules[13] and is typically administered orally to treat mild insomnia and anxiety in combination with hops. It is assumed to activate GABA through Valerenic acid as the active ingredient[13].

Comparative trials between valerian-hops and synthetic sedatives/anxiolytics are rare. One such study compared the efficacy of a valerian-hops combination to that of diphenhydramine in insomnia over 6 weeks. They revealed modest improvement in sleep outcome measurements in both treatment arms[14]. However, no previous studies have compared the efficacy of single doses of valerian-hops to sedating antihistamine in terms of subjective sleep measures.

Therefore, the objective of the current study is to evaluate and compare the effect of a single dose of valerian-hops against a single dose of a widely used antihistamine, chlorpheniramine, when modulating subjective sleep measures among refugees with insomnia. Subjective sleep parameters were evaluated according to Leeds Sleep Evaluation Questionnaire (LSEQ). Other studied parameters were: sleep latency, sleeping hours, sedation, anxiety and self-rated clinical evaluation.

Methods

Study design and outcome measures

Initially, refugees were screened for insomnia clinically and by using the Insomnia Severity Index (ISI). Afterwards, insomniac refugees were randomly assigned to receive a single dose of valerian-hops, chlorpheniramine or a placebo. The outcome measures were difference in sleep quality according to the (LSEQ), anxiety, sedation, sleep latency, actual hours slept and self-rated clinical improvement. Ethical approval was obtained from the institutional review board (IRB) at King Hussain Hospital. Potential participants were provided with details on the study and had to sign a detailed IRB approved consent form prior to participation. Each participant was informed about his/her right to withdraw from the study at any time.

Sample and sampling method

Adult refugees living in two cities in Jordan (Amman and Mafraq) were approached during their visit to the Caritas Medical Centre.

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At the screening phase, refugees with a prior history of psychological or mental illnesses and ones using anxiolytics or antidepressants or any drugs affecting the central nervous system were excluded. Pregnant or lactating females were also excluded.

Intervention

After screening completion, insomniac refugees were asked about their willingness to participate in the trial. Willing participants were randomly assigned to receive a Cirkulin® Valerian-hops combination (320 mg of valerian root dry extract + 80 mg of hop stabile dry extract), chlorpheniramine 4 mg or a placebo. Randomization was performed by sequencing patients entering to the physician by using numbered closed envelopes. The prescribing physicians asked all the participants to take the single dose two-hour prior to their bed time.

Each participant was asked to complete an LSEQ at awakening. Sedation and anxiety visual analogue scales were filled one hour after the dose, after awakening and 24 hours after dose administration. Data collection and entry was performed by independent researchers blind to the interventions.

Sample size calculations

For the purpose to determine the number of participants need in each study groups, statistical G power calculation was used and revealed the need for at least 44 participants in each group; this was based on 0.07 Eta Squared, and power of 0.80. However, the authors decided to include as much as possible participants equal or greater than 44 in each group.

Study instruments

In addition to demographical and clinical details, the Arabic versions of ISI, LSEQ, the anxiety visual analogy scales, the sedation visual analogue scale, and the treatment evaluation were employed.

The ISI was developed by Morin[15] and consists of seven questions with Likert type choices ranging from 0 to 4; a higher score indicates more sleeping problems. The total possible score for each participant ranged from 0 to 28. Based on a previous literature participants, scoring 10 or more were considered to be insomniacs[16]. Prior research utilized the Arabic version of ISI, which was showed to be reliable with an internal consistency of 0.84[17]. In the current study, ISI was showed to have good reliability with a Cronbach's alpha score of 0.89.

The LSEQ was used to assess sleeping patterns among refugees[18]. The scale was self-reporting and consisted of ten 100-mm visual analogue types of questions, which measure four dimensions of sleep: ease of getting to sleep (GTS) three questions, quality of sleep (QOS) two questions, awakening from sleep (AFS) two questions, and behavior following wakefulness (BFW) three questions. Each participant responded by marking each visual analogue line from 0 to 100 mm. The mark position indicated the changes that occur in sleeping; marks closer to the left indicate improvement, closer to the right indicate impairment, and closer to the middle indicates no changes. The LSEQ was translated to the Arabic language using the standardized back translation method, and each factor showed good reliability with Cronbach's alpha scores ranging from 0.90 to 0.94.

In addition to these measures, a visual analogue scale for each anxiety and sedation that ranged from 0 to 10 was used. The higher score indicates higher anxiety and sedation. Moreover, at 24 hours each participant was asked to mention the minutes they needed to sleep, and the hours of sleeping during that night. Additionally, participants were asked for asked for treatment evaluation, which ranged from one to three (1 for no improvement, 2 for slight improvement, and 3 for marked improvement.)

Statistical analysis

All refugees' continuous data included the LSEQ, with sedation, anxiety and insomnia scores showing as normally distributed. SPSS statistical package version 21 was used to analyze the data. Descriptive statistics were used to analyze frequencies and standard deviations, means and differences in insomnia at screening level.

One-way ANOVA was used to examine the differences in the LSEQ, sedation scores, anxiety, time to sleep, and time of sleeping between the three groups (i.e. valerian-hops, chlorpheniramine and placebo). The Kruskal-Wallis test was used to examine the differences between the three groups in each treatment evaluation. The significant level was less than 0.05 for the statistical tests.

Results

A total of 373 were assessed for their eligibility. A total of 111 candidates were excluded. Therefore, two hundred sixty participants were randomized for the three study groups. A total of one hundred ninety participants successfully completed the study and their data were analyzed. Please refer to the flow chart (Figure 1).

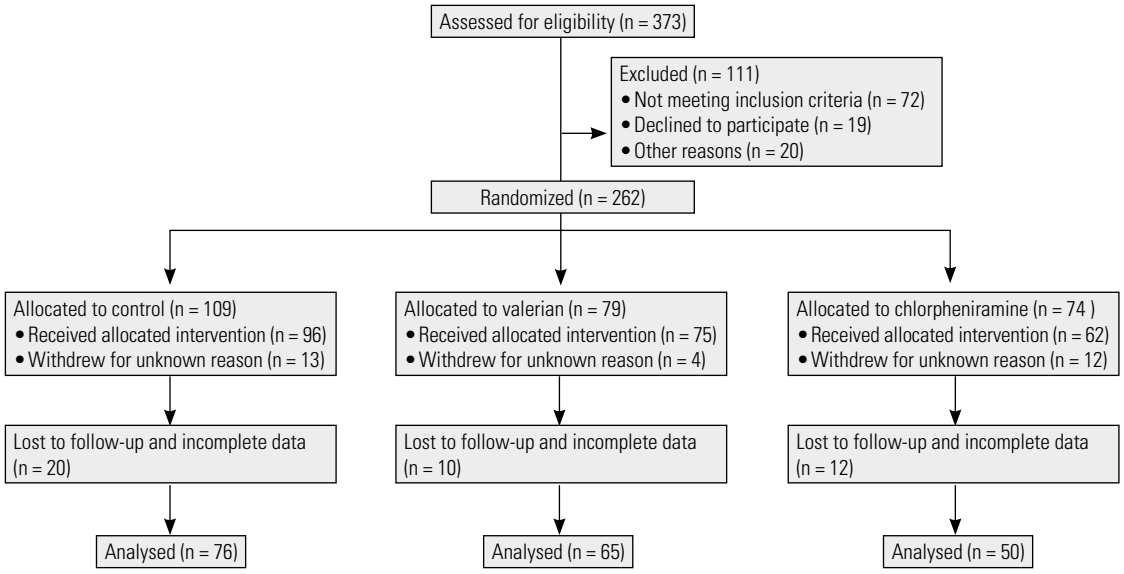

Figure 1. Study flow chart showing participants randomization.

Demographical and clinical details

The mean age of intervention participants was 45.0 (SD = 13.61). As shown in Table 1, the majority of refugees that participated in the study lived in Amman (n = 124, 64.9%), were female (n = 114, 59.7%), married (n = 148, 77.5%), had less than a secondary school education (n = 119, 62.3%), were unemployed (n = 114, 59.7%), had Syrian nationality (n = 131, 68.6%), were non-smokers (n = 113, 59.2%), were not diagnosed previously with any chronic illness namely hypertension, diabetes and cardiac diseases (n = 110, 57.6%), and had medications for chronic illnesses available (anti-hypertensives, oral hypoglycemic agents, etc.) (n = 185, 96.9%).

Table 1. Demographical details of intervention part of study participants

Factors	Categories	Number (percentage)
City	Amman	124 (64.9%)
	Mafraq	67 (35.1%)
Gender	Female	114 (59.7%)
	Male	77 (40.3%)
Marital status	Married	148 (77.5)
	Single	43 (22.5%)
Education level	Less than secondary	119 (62.3%)
	Secondary school or higher	72 (37.7%)
Employment	Yes	161 (84.3%)
	No	30 (15.7%)
Smoking status	Smoker	78 (40.8%)
	Non-smoker	113 (59.2%)
Previous chronic illness (s)	No	110 (57.6%)
	Yes	81 (42.4%)
Medication availability	No	6 (3.1%)
	Yes	185 (96.9%)
Nationality	Syrian	131 (68.6%)
	Iraqi	60 (31.4%)

LSEQ at awakening

As shown in Table 2, the LSEQ was completed at awakening. One-way ANOVA test was used to examine the differences in four factors based on the type of intervention that refugees received.

The ANOVA test showed significant differences in GTS scores between the three groups F (2,189) = 22.64, P = 0.001, QOS scores F (2,189) = 60.19, P = 0.001, AFS F (2,189) = 22.55, P = 0.001, and BFW F (2,189) = 28.52, P = 0.001. The Scheffe *post hoc* test showed that the chlorpheniramine group had a significantly higher score of GTS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops group.

Post hoc showed that there were differences in QOS; the chlorpheniramine group had a significantly higher score of QOS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops groups.

In addition, the chlorpheniramine group had a significantly higher score of AFS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops groups.

Moreover, valerian-hops had a significantly higher score of BFW compared to the placebo group (p = 0.001) and lower scores compared to chlorpheniramine (p = 0.001). In addition, the chlorpheniramine group had a significantly higher score of BFW compared to the placebo group (p = 0.045).

Table 2. Differences in study measures based on the intervention received

Factors	Group	Mean score at 1 hour	Mean score at awakening	Mean score at 24 hours
Leeds (GTS)	Control		4.82	
	Valerian-hops		5.02	
	Chlorpheniramine		6.28	
Leeds (QOS)	Control		4.85	
	Valerian-hops		5.33	
	Chlorpheniramine		6.82	
Leeds (AFS)	Control		4.79	
	Valerian-hops		5.26	
	Chlorpheniramine		6.32	
Leeds (BFW)	Control		4.80	
	Valerian-hops		5.37	
	Chlorpheniramine		6.64	
Sedation	Control	5.25	5.29	5.15
	Valerian-hops	5.18	4.92	4.90
	Chlorpheniramine	5.88	4.98	5.03
Anxiety	Control	5.10	5.01	5.15
	Valerian-hops	4.63	4.76	4.90
	Chlorpheniramine	4.35	4.17	4.62
Sleep latency in minutes	Control		71.83	
	Valerian-hops		64.11	
	Chlorpheniramine		36.08	
Total hours slept	Control		6.80	
	Valerian-hops		6.89	
	Chlorpheniramine		6.58	

Sedation at 1 hour, at awakening and at 24 hours

As shown in Table 2, sedation was measured at 1 hour, after awakening and at 24 hours. One-way ANOVA was performed to examine the differences between the three groups in sedation at one hour, at awakening and at 24 hours.

One-way ANOVA showed that there were significant differences between the three groups in one hour F (2,189) = 25.13, P = 0.001, at awakening F (2,189) = 6.51, P = 0.001 but not in 24 hours F (2,189) = 1.82, P = 0.164.

The *post hoc* test at one hour showed that the chlorpheniramine group had a significantly higher score compared to both placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between valerian-hops and placebo groups at one hour.

Moreover, *post hoc* at awakenings in the placebo group had a significantly higher score compared to both valerian-hops (p = 0.004) and chlorpheniramine groups (p = 0.036). However, there were no significant differences between the valerian-hops and chlorpheniramine group at awakenings.

Anxiety at one hour, at awakening, and at 24 hours

As shown in Table 2, anxiety was measured at 1 hour, at awakenings and at 24 hours. One-way ANOVA was utilized to examine the differences between the three groups' anxiety levels at one hour, at awakenings and at 24 hours.

One-way ANOVA showed that there were significant differences between the three groups in one hour F (2,189) = 8.06, P = 0.001, at awakenings F (2,189) = 10.99, P = 0.001 and at 24 hours F (2,189) = 5.63, P = 0.004.

The *post hoc* test at one hour showed that the placebo group had significantly higher scores compared to both valerian-hops (p = 0.034) and chlorpheniramine groups (p = 0.001). However,

there were no significant differences between the valerian-hops and chlorpheniramine groups at one hour.

Moreover, the *post hoc* test at awakenings in the placebo group had a significantly higher score compared to both the chlorpheniramine (p = 0.001) and valerian-hops groups (p = 0.007). However, there were no significant differences between the valerian and placebo groups at awakenings.

In addition, at 24 hours, the placebo group had a significantly higher score compared to chlorpheniramine (p = 0.004). However there were no significant differences between the Valerian and placebo groups, and between the valerian-hops and chlorpheniramine groups at 24 hours.

Sleep latency and total hours slept

As shown in Table 2, time to sleep and time of sleeping were reported after awakening. For the purpose of examining latency and actual differences in time to sleep in minutes and hours between the three groups, a one-way ANOVA was used. The test showed that there were significant difference between the three groups F (2,189) = 13.11, p = 0.001. The *post hoc* test showed that the placebo group had a significantly higher latency time compared to the chlorpheniramine group (p = 0.001). In addition, the valerian-hops group had longer latency time compared to the chlorpheniramine group (p = 0.001). There was no significant difference between placebo and valerian-hops groups. The results for the time of sleeping differences between the groups showed no significant differences.

Participants' evaluation

As shown in Table 3, each participant in the intervention group was asked to complete a treatment evaluation. There were three options: no improvement, slight improvement and marked improvement.

The Kruskal-Wallis test was used to examine the differences in patients' evaluations. The results indicate that there was a significant difference between them. Between the three groups (Chi square = 12.45, p = 0.002) the higher mean rank was for the chlorpheniramine group (mean rank = 115.62), followed by the valerian-hops group (mean rank = 96.28), and the lowest was for the placebo group (mean rank = 82.86).

Table 3. Treatment evaluation

Group	Participant's self-evaluation		
	No improvement	Slight improvement	Marked improvement
Control	25	50	1
Valarian-hops	22	28	15
Chlorpheniramine	14	13	23
Total number	61	91	39

Discussion

This is the first study that has evaluated and compared the efficacy of valerian-hops and chlorpheniramine among insomniac refugees. Although our results demonstrated that neither valerian-hops nor a chlorpheniramine single dose improved sleep, valerian-hops combination demonstrated a significantly better sleep quality compared to chlorpheniramine.

The efficacy of valerian in improving sleep remains controversial. Previously, some studies have reported improved sleep outcomes with single or multiple doses of valerian[19-21]. On the contrary, our findings are consistent with recent research demonstrating nonsignificant improvement in sleep measures[22,23].

This controversy could be explained by the different study sample, study design, extract type and valerian dose. All previous trials recruited patients with insomnia or healthy volunteers whereas in the current study all participants were recently displaced refugees.

No previous study compared valerian-hops with antihistamine single doses, however, a single study that compared valerian-hops with diphenhydramine demonstrated modest improvements on subjective sleep measures after 6 weeks[24]. Based on our observation that many insomniac subjects use a single dose of sedative/anxiolytics. This is the first study comparing a single dose of valerian-hops combination to antihistamine in improving subjective sleep measures among insomniac refugees.

The anxiolytic and sedative profiles of the two treatments can be explained as follows. Valerian-hops produces an "as needed" anxiolysis that is evident only after one hour compared to the extended anxiolysis and sedative effect of chlorpheniramine. This could be attributed to valerenic acid that is detectable in the serum only within the first hour of administration[25].

This also explains the nonsignificant latency time reduction seen with valerian-hops compared to chlorpheniramine. Moreover, this favorable pharmacokinetic profile prevents residual effects manifested by cognitive and psychomotor side effects with sedating antihistamines.

The study has several weaknesses, as it relied only on subjective sleep measures. Furthermore, the randomization process was not according to standard procedure which could have led to possible bias. Also, the single dose design may not reflect the maximal potential benefit of valerian-hops. A cross-over design was not implemented. Furthermore, refugees are a highly anxiety-prone population, therefore, the results of this study may not be applied to insomniac patients from the normal population. In conclusion, insomnia represents a serious challenge for refugees. Valerian-hops combination revealed better sleep quality than sedating antihistamine. Further studies are needed with multiple dosing design to reveal the potential benefit of this herb among refugees.

Conclusion

Our findings demonstrated that Valerian-hops combination may provide better sleep quality than antihistamines due to its sufficient anxiolytic effect. The study aimed to raise awareness for the need to study over the counter medicines. It may lead to better controlled randomized trials.

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Disclosure

The authors declare no conflict of interest.

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